



PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty Docket No. A01406  
KC

In re application of:  
James Charles Bohling et al.

Serial No.: 10/636,148 : Group Art Unit: 1711

Filed: August 7, 2003 : Examiner: Morton Foelak

For: RESIN FOR SOLID PHASE SYNTHESIS

DECLARATION UNDER 37 C.F.R. § 1.132

I, James C. Bohling, of 1904 Stirling Drive, Lansdale, PA, declare and say as follows:

1. I have been employed at the Rohm and Haas Company since 1999. I have a Bachelor of Science degree in Chemistry from Hope College (1992), a Ph.D. in Physical Organic Chemistry from Boston College (1997), and completed Post Doctoral fellowship at the University of Utah (1999). I have been involved with our Ion Exchange Business since 1999 and the Advanced Biosciences business since 2003. My job responsibilities have included research and development in the area of improved resin beads useful in solid-phase organic synthesis. I am currently a Senior Scientist.

2. I have been the coinventor of 19 U.S. patent applications filed during my tenure at Rohm and Haas Company.

3. As a co-inventor of the present invention, I am thoroughly familiar with its subject matter and background. I have read the Official Action dated August 19, 2004 in the above-mentioned US patent application (Serial No. 10/636,148). I have reviewed the cited reference, Meitzner et al.

4. In November, 2004, at the Rohm and Haas Company research laboratories in Spring House, Pennsylvania, I supervised preparation of polymeric beads made by a procedure disclosed in Meitzner, but with an amount of crosslinker within the scope of the present application. Beads were made using 1.5% and 2%

crosslinker, and 35% porogen {4-methyl-2-pentanol (MIBC)}; see Meitzner, Col. 8, line 61 to Col. 9, line 2. The details of the procedure are presented below:

Summary of Process Run:

Run process in a 2L round bottom flask with a light nitrogen sweep. Sparge monomer phase with N<sub>2</sub>. Stir @ 275 rpm during hold period. Ramp process to 86°C over 60 minutes, hold for 6 hours. Wash with tetrahydrofuran (THF) and methanol.

Preparation of Aqueous Solution:

Weigh 638g of DI water and charge in round bottom flask. Stir @ 150rpm and heat to 80°C under N<sub>2</sub> sweep. Once temperature is reached, charge 3.175g of MHEC- 8000 (hydroxyethyl methyl cellulose) slowly in flask. Hold for 60 minutes @ 80°C. After hold time cool Aqueous solution to 25°C - 30°C. Weigh out and charge the following to the flask: 0.036g WA-100 (sodium lauryl sulfate). Stir for 30 minutes. Sweep with N<sub>2</sub>.

Preparation of Monomer Solution:

Prepare monomer in a beaker, charge the following:

For 2% DVB: 10.6g DVB-55% (divinylbenzene), 279.6g styrene, 3.87g of 75% benzoyl peroxide (2.90g active) and 156g of 4-methyl-2-pentanol (MIBC);

For 1.5% DVB: 7.9g DVB-55% (divinylbenzene), 282.3g styrene, 3.87g of 75% benzoyl peroxide (2.90g active) and 156g of 4-methyl-2-pentanol (MIBC).

Adjust agitator speed to 275rpm before charging monomer mix to flask. Stop agitator and charge monomer to Aqueous solution. After charging monomer mix resume agitation and stir for 30 minutes @ 25°C. Ramp temperature to 86°C over 1 hour. Hold @ 86°C for 6 hours.

Washing:

After cooling place resin into Buchner funnel and wash with 8 bed volumes of THF followed by 4 bed volumes of methanol with stirring while draining. Dry the resin in vacuum oven and screen to 150-90 micron.

5. In August, 2002, I obtained beads made on a commercial scale in Soma, Japan by scaling up the procedure of the present invention, as shown below:

Summary of Process Run:

Run process in a 2L round bottom flask with a light nitrogen sweep. Sparge monomer phase with N<sub>2</sub>. Stir @ 275 rpm during hold period. Ramp process to 84°C over 60 minutes, hold for 12 hours. Treat with Cellulase for 4 hours.

Preparation of Aqueous Solution:

Weigh 638g of DI water and charge in round bottom flask. Stir @ 150rpm and heat to 80°C under N<sub>2</sub> sweep. Once temperature is reached, charge 3.175g of MHEC- 8000 slowly in flask. Hold for 60 minutes @ 80°C. After hold time cool Aqueous solution to 25°C - 30°C. Weigh out and charge the following to the

flask: 2.4 g 50% NaOH, 2.5g Boric Acid, 0.036g WA-100(SLS), and 0.1g Sodium Nitrite. Stir for 30 minutes.

Preparation of Monomer Solution:

Prepare monomer in a beaker, charge the following: 6.55g DVB (Divinylbenzene), 440.0g Styrene, 5.8g Trigonox (Trig 21). Transfer mix to an Addition Funnel and sparge for 40 minutes.

Adjust agitator speed to 275rpm before charging monomer mix to flask. Stop agitator and charge monomer to Aqueous solution. Position Addition Funnel over flask so as not to introduce air to monomer solution. After charging monomer mix resume agitation and stir for 30 minutes @ 25° C. Ramp temperature to 84° C over 1 hour. Hold @ 84° C for 12 hours.

Cellulase Treatment:

After 12 hour hold cool batch to 45° C, adjust pH to 5.0 with HCL. (37%) Charge 19.05g of Cellulase 4000 to batch, stir for 2 hours @ 45° C. After the 2 hour hold add a second charge of Cellulase 4000 and hold for 2 hours @ 45° C. At the end of hold period cool down to room temperature, remove from flask and wash with DI water.

6. Beads produced by the foregoing procedures were compared, using light microscopy. Beads were prepared for microscopy by placing them, dry, onto a microscope slide and analyzing on a Standard Zeiss Stemi 2000C microscope, with the images captured with a Media Cybernetics Cool Snap Digital camera and Image Pro 4 software. Photos were obtained at 10x, (both 5x and 2x lenses in place). Light was transmitted indirectly from below.

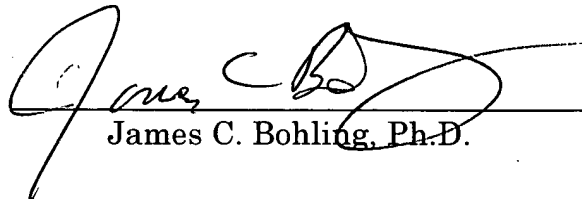
7. Photomicrographs are attached as Figures 1 to 5. Identification of the figures is as follows:

	Crosslinker (DVB)	Porogen (MIBC)	Comments
Figure 1	1%	0%	method of present application
Figure 2	1.5%	35%	Meitzner process, 1.5% DVB
Figure 3	1.5%	35%	enlargement of Fig. 2
Figure 4	2%	35%	Meitzner process, 2% DVB
Figure 5	2%	35%	Meitzner process, 2% DVB

Each Figure bears a calibration line to indicate the scale of objects in the photograph.

8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful

false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United State Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



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